Immunotherapy combinations

Checkpoint inhibitor (8). Phase I testing has begun. Similar preclinical evidence supports the evaluations of ALK-TKIs plus an immune checkpoint inhibitor (8). Phase I testing has begun.

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Randomized phase III trials of an EGFR-TKI versus an immune checkpoint inhibitor have been completed (10). The regimen was feasible and well tolerated with promising antitumor activity. A randomized phase III trials of an EGFR-TKI versus an immune checkpoint inhibitor has been launched. Similar preclinical evidence supports the evaluations of ALK-TKIs plus an immune checkpoint inhibitor (8). Phase I testing has begun.

Immunotherapy combinations. Optimizing the immune system to attack tumors will require exploiting its diverse components. Employing a dual immune approach with anti-PD-1 plus an anti-CTLA-4 agents has been successful in treating advanced melanoma. In lung cancer phase III trials of PD-1 and CTLA-4 inhibitors have been activated based on encouraging phase I data (12).

Meanwhile, early phase trials evaluating immune checkpoint inhibitors with immune checkpoint agonists, cytokines, and vaccines are ongoing to determine the safest and most effective combinations.

Overall we are optimistic that combination regimens that can harness the immune system together with tumor directed therapies will lead to improved clinical benefit. Continued pursuit of optimal combinations will however require increased insight into the complex interactions between the tumor, the immune response and pharmacological interventions.

References

and sensitizes established pancreas tumors to gemcitabine. LIF activates a unique set of downstream pathways, distinct from IL-6 and other members of this family of cytokines. This pathway may account for K-Ras' unique ability to promote stem-ness. The existence of a new effector pathway specific for KRAS therefore offers new opportunities for therapeutic intervention.

Immunomodulatory effects of radiotherapy: Magical effects of the healing beam?

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Immunotherapy is changing the management of metastatic lung cancer. Checkpoint inhibitors have demonstrated promising response in non-small cell lung cancer and are emerging as amongst the most efficacious anticancer agents ever discovered. Checkpoint inhibitors are aimed at reversing mechanisms of T-cell suppression by blocking signaling through regulatory T-cell co-receptors (e.g. CTLA-4 or PD-1) or blocking T-cell suppressive enzymes (e.g. Indolamine 2,3 Dioxygenase (IDO)). These therapies can achieve durable long-term remissions, however, most patients fail to respond, and some can experience significant immune-mediated toxicities (1-3). Combinatorial strategies employing immunotherapy and standard-of-care therapies may increase the efficacy of immunotherapy and extend its benefits to a larger proportion of patients. Little data is available on how best to achieve this goal.

Radiotherapy (RT) is an ideal candidate for combinatorial immunotherapy strategies. In addition to debulking tumor and releasing tumor antigens, RT has well-established immunomodulatory effects (4). These interdependent and overlapping effects include increasing homing and effector function of tumor infiltrating lymphocytes (TILs) including T-cells (5) and natural killer (NK) cells (6), increasing the diversity of the T-cell response (7), destruction of immunosuppressive cells in the tumor microenvironment (8), induction of immunogenic cell death (9,10), increased dendritic cell (DC) trafficking and presentation of tumor antigen (11), and upregulation of immunogenic cell surface receptors (12) and stress ligands (6). Additionally our recent data demonstrate that RT can induce chemokines such as CCL3, 4, and 5 and the critical nature of these chemokines to an anti-tumor immune response and the effectiveness of checkpoint blockade immunotherapy has recently been highlighted (13). The immunomodulatory effects of radiotherapy are complex and some of these effects can be suppressive such as induction of TGF-beta (14), accumulation of immunosuppressive cells (15), upregulation of PD-L1 (16), and upregulation of IDO.

Clinical reports confirm the safety and efficacy of multimodality strategies employing RT and CpG or IL-2 immunotherapy (17,18). There is also data to suggest synergy between RT and checkpoint inhibition (16,19,20). Dozens of clinical trials testing such combinatorial strategies are underway with countless others in preparation, which will together likely accrue thousands of patients. There is considerable variability in “standard-of-care” RT regimens and combinatorial strategies could employ a wide variety of dose/fractionation regimens, sequencing/timing regimens, and even RT quality (i.e. photons vs. protons). There is limited mechanistic data available to guide how to best combine these modalities (21,22). These variables can substantially alter the efficacy of combined RT + immunotherapy strategies. A framework for appropriately combining these therapies is needed and will have an immediate impact on patient care. It is possible that different immunotherapies and different tumors will behave differently in response to these RT variables. The mechanistic immune effects of RT and immunotherapy are complex. Identifying the best strategies to combine these immune effects will likely be similarly complex.

References